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Assessing fluid responses after coronary surgery: role of mathematical coupling of global end-diastolic volume to cardiac output measured by transpulmonary thermodilution

Rose-Marieke B.G.E. Breukers[a], Rob B.P. de Wilde[b], Paul C.M. van den Berg[b], Jos R.C. Jansen[b], Theo J.C. Faes[c], Jos W.R. Twisk[d] and A.B. Johan Groeneveld[a]

Background **Mathematical coupling may explain in part why cardiac filling volumes obtained by transpulmonary thermodilution may better predict and monitor responses of cardiac output to fluid loading than pressures obtained by pulmonary artery catheters (PACs).**

Methods **Eleven consecutive patients with hypovolaemia after coronary surgery and a PAC, allowing central venous pressure (CVP) and continuous cardiac index (CCIp) measurements, received a femoral artery catheter for transpulmonary thermodilution measurements of global end-diastolic blood volume index (GEDVI) and cardiac index (CItp). One to five colloid fluid-loading steps of 250 ml were done in each patient ($n = 48$ total).**

Results **Fluid responses were predicted and monitored similarly by CItp and CCIp, whereas CItp and CCIp correlated at $r = 0.70$ ($P < 0.001$) with a bias of 0.40 l min^{-1} m^{-2}. Changes in volumes (and not in CVP) related to changes in CItp and not in CCIp. Changes in CVP and GEDVI similarly related to changes in CItp, after exclusion of two patients with greatest CItp outliers (as compared to CCIp). Changes in GEDVI correlated better to changes in CItp when derived from the same thermodilution curve than to changes in CItp of unrelated curves and changes in CCIp.**

Conclusions **After coronary surgery, fluid responses can be similarly assessed by intermittent transpulmonary and continuous pulmonary thermodilution methods, in spite of overestimation of CCIp by CItp. Filling pressures are poor monitors of fluid responses and superiority of GEDVI can be caused, at least in part, by mathematical coupling when cardiac volume and output are derived from the same thermodilution curve. *Eur J Anaesthesiol* 26:954–960**

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Keywords: continuous pulmonary thermodilution cardiac output, fluid responses, mathematical coupling, transpulmonary thermodilution cardiac output, volumes versus pressures

[a]Department of Intensive Care and Institute for Cardiovascular Research, [b]VU University Medical Center, Amsterdam, and Department of Intensive Care, [c]Department of Physics and Medical Technology and [d]Department of Clinical Epidemiology and Biostatistics, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to A.B. Johan Groeneveld, MD, PhD, FCCP, FCCM, Department of Intensive Care, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
Tel: +31 20 4444178; fax: +31 20 4442392; e-mail: johan.groeneveld@vumc.nl

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Introduction

Fluid loading is a common therapeutic step after cardiac surgery, and predictors and monitors of fluid responses of the heart are continuously explored. Transpulmonary thermodilution (PiCCO)-derived blood volumes such as the global end-diastolic blood volume index (GEDVI) may better predict and monitor preload-dependent fluid responses of cardiac output than central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) obtained by a pulmonary artery catheter (PAC) [1–13]. Indeed, transmitted airway pressure in mechanically ventilated patients may confound filling pressures as indicators of fluid responses. Volumes may be less dependent on mechanical ventilation than pressures (and dynamic indicators) [7,9,12], but superiority of the former can be doubted. Indeed, observations on the superior predictive and monitoring value of transpulmonary volumes for fluid responses may be confounded by a shared measurement error and mathematical rather than physiologic coupling, when both volumes and cardiac output are derived from the same transpulmonary thermodilution curve [3]. For instance, echocardiographic dimensions may less well predict transpulmonary cardiac output than transpulmonary volumes [6]. Even though cardiac output may vary independently from volumes by infusion of inotropes or ß-blockers suggesting independent variance in spite of mathematical coupling [14,15], the effect of the latter on assessment of fluid responses, when volumes and cardiac output change in similar directions, has been addressed only once, unsupported by data [10].

Mathematical coupling can be evaluated by using an independent measurement [3,16–18]. For comparison with cardiac output measured by transpulmonary thermodilution, which agrees with that obtained by pulmonary artery thermodilution [1,4,10,19–25], we used the continuous thermodilution cardiac output measurement

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technique via a PAC. The latter does not require repeated injections and is an acceptable alternative to the intermittent bolus technique, at least, perhaps, in the absence of tricuspid regurgitation and rapid rewarming, and provided that the relative slowness of the system is taken into account [26–34]. Continuous methods are attractive in monitoring fluid responses and the continuous pulmonary and intermittent transpulmonary thermodilution cardiac output responses proved almost interchangeable in that respect, prior to coronary artery surgery, in the single available comparison [10]. However, methods may also require comparison after surgery, when haemodynamic stability may be less [2,23,24,32–34].

The goal of the current study was to compare intermittent transpulmonary (PiCCO) and continuous pulmonary (PAC) thermodilution methods and associated static cardiac filling indicators in predicting and monitoring fluid responses, in mechanically ventilated patients after coronary artery surgery. This was done to test the hypothesis that mathematical coupling with cardiac output accounts, at least in part, for the alleged superiority of GEDVI over pressures in predicting and monitoring fluid responses.

Patients and methods

Eleven consecutive patients undergoing elective coronary artery bypass grafting below 85 years of age were included and studied within 2 h after surgery in the intensive care unit. The Local Ethics Committee approved the study protocol and written informed consent was obtained from all patients before surgery. Inclusion criteria were life expectancy more than 24 h and presumed hypovolaemia and tolerance to intravenous (i.v.) fluids, arbitrarily defined by PAOP and CVP less than 13 mmHg and a continuous cardiac index measured in the pulmonary artery (CCIp) less than $4.0\,l\,min^{-1}\,m^{-2}$. Exclusion criteria were surgical bleeding greater than $100\,ml\,h^{-1}$, clinical evidence for pulmonary oedema, known aneurysms of thoracic or abdominal aorta and presence of atrial fibrillation. All patients underwent cardiopulmonary bypass. There were no visible V waves in the CVP curve, thereby disfavouring haemodynamically important tricuspid regurgitation. Doses of drugs, including vasoactive agents, were given according to local guidelines. Patients were sedated with propofol ($1\,mg\,kg^{-1}\,h^{-1}$) or midazolam ($0.1\,mg\,kg^{-1}\,h^{-1}$) and sufentanil ($0.5\,\mu g\,kg^{-1}\,h^{-1}$). Patients were on volume-controlled ventilation with tidal volumes of $10\,ml\,kg^{-1}$ and a positive end-expiratory pressure (PEEP) of $5\,cmH_2O$. Ventilation frequency was adjusted between 10 and 13 breaths min^{-1} to maintain the arterial PCO_2 in the normal range (4.5–6.0 kPa).

Pulmonary artery catheter

A thermal filament-rapped pulmonary artery thermodilution catheter (8.5-Fr, CCO/VIP, Edwards Life Sciences, Santa Ana, CA, USA) for continuous cardiac output monitoring had been preoperatively inserted via the internal jugular vein. The catheter was connected to a computer (Vigilance, Edwards Life Sciences, Irvine, CA, USA), displaying continuous cardiac output data at 0.5–1 min intervals. After pooling of data, measured at 1–2 min intervals and normalized for individual means ($n = 59$), the reproducibility of CCIp, expressed as the coefficient of variation around the mean, was 4.2% in our patients. The PAC was also used to determine PAOP and CVP at the end of expiration, after calibration and zeroing to atmospheric pressure, at the mid-chest level, after, for the PAOP, proper wedging, and with patients in the supine position.

Transpulmonary thermodilution

The transpulmonary thermodilution technique (PiCCO, Pulsion Medical, Munich, Germany) was used to determine GEDVI, representing the sum of volumes of the cardiac chambers at end diastole [4,6,11,15,35]. The GEDVI is derived from the transpulmonary cardiac index (CItp) multiplied by the difference in mean transit time of the thermal indicator and its down-slope time. We found in the 132 recorded individual of triplicate transpulmonary measurements in this study, which were pooled after normalization for individual mean values, a reproducibility, expressed as the coefficient of variation around the mean, of 6.7% for CItp and of 11.3% for GEDVI, in accordance with the literature [1,4,11,19,21]. Body surface area calculated from weight and height was used to normalize measured variables (SVI equals stroke volume index).

Study protocol

Within 2 h after arrival in the intensive care unit, a 5F thermodilution catheter (Pulsiocath PV 2015; Pulsion Medical, Munich, Germany) was inserted via the femoral artery into the aorta and connected to the PiCCO computer. Demographic data, including the EuroSCORE and body surface area, calculated from height and weight were collected. At baseline ($T = 0$), heart rate (HR), mean arterial pressure (MAP), PAOP, CVP, GEDVI, CItp and CCIp were measured. To this end, three central venous injections of 20 ml of cold (<8°C) saline were done, regardless of the respiratory cycle, and averaged values were taken. Five fluid-loading steps of 250 ml each (1250 ml in total) were performed at 30 min intervals (from $T = 0$ to $T = 5$), in eight patients ($n = 40$ steps). One patient received 250 ml of fluids (one step), one patient 750 ml (three steps), and one patient 1000 ml (four steps). Fluid loading was discontinued in the three latter patients, in case of sudden changes of MAP, increasing more than 10 mmHg, PAOP, increasing more than 6 mmHg or CCIp, increasing more than $2.1\,l\,min^{-1}\,m^{-2}$ over values in preceding step. After each 15 min loading step, 15 min were allowed for reaching a new steady state before haemodynamic variables were

measured [28], and the CCIp was taken before CItp measurements. If coagulation was impaired, 250 ml of fresh frozen plasma ($n = 11$ fluid steps) was given. In all other cases ($n = 37$ fluid steps), a starch (MW 130) solution (Voluven, Fresenius, Germany) was used. Heart rate was recorded with one of the standard leads of the electrocardiogram. Two patients were sequential atrial–ventricular pacemaker-dependent during the study protocol; the pacemaker frequency was set at 80 beats min^{-1}. Doses of continuously administered vasoactive and sedative drugs and ventilator settings were unchanged during the study protocol.

Statistical analysis

We expected about 50% rises more than 5% or at least 10% (with no-rises $\leq$5 and $<$10%, respectively) in cardiac output among fluid-loading step. The cut-offs were chosen to account for the volumes administered and the literature on fluid responsiveness [9,10,12,13]. Generalized estimating equations, taking repeated measurements in the same patients into account, were used to evaluate changes over time, to study the concordance of fluid responses among cardiac output techniques and to study the value of baseline values to predict and changes in variables to monitor fluid responses by either technique. The type of fluid was entered as a covariate. The CItp and CCIp were then compared by means of Bland and Altman plots of differences versus means, yielding bias, precision (SD) and limits of agreement (bias $\pm$ 2SD), and were correlated with help of linear regression [36]. This allowed identifying the patients with the greatest potential errors in CItp and it was reasoned that their exclusion would decrease mathematical coupling to GEDVI and overestimation of correlations, if any. We also calculated bias and limits of agreement with help of a standard deviation corrected for that of differences between techniques within each patient, to account for repeated measurements [36]. To judge the effect on assessing fluid responses by mathematical coupling between GEDVI and CItp versus CCIp, we compared relations between pressure, volume and cardiac output (changes), prior to and after fluid loading, prior to and after exclusion of CItp outliers (versus CCIp), and prior to and after averaging of triplicate measurements. Partial linear correlation coefficients, with patient numbers as a covariate to account for repeated measurements, were calculated for the relations and compared after z transformation. Exact two-sided P values greater than 0.001 are given and considered statistically significant if less than 0.05. Data were summarized as mean $\pm$ standard deviation (SD), since they were normally distributed (Kolmogorov–Smirnov test).

Results

Patient characteristics are described in Table 1. Table 2 summarizes results of haemodynamic measurements, prior to and after each fluid-loading step.

Fluid responses

In Table 3, fluid steps have been pooled, according to rises and no-rises for both cardiac output techniques, defined by two cut-off values. Fluid responses were similar, when judged from changes in CItp or CCIp, and there was a high concordance (69%) between techniques for responses more than 5% and at least 10% ($P = 0.001$). The table shows that filling pressures (and MAP) were of poor value in predicting and monitoring fluid responses. In contrast, changes in GEDVI paralleled fluid responses, but only when judged by CItp, regardless of type of fluid.

Comparing CItp to CCIp and relations with pressures and volumes

Figure 1 shows the relationship between CItp and CCIp for pooled data ($r = 0.70$, $P < 0.001$; $n = 59$). Pooled changes in time correlated also ($r = 0.44$, $P = 0.002$; $n = 48$). The bias between techniques was 0.40 l min^{-1} m^{-2} and limits of agreement were -0.68 and 1.48 l min^{-1} m^{-2}, since precision was 0.54 l min^{-1} m^{-2}. After correction for repeated measurements, bias was 0.33 l min^{-1} m^{-2} and limits of agreement (bias $\pm$ 2SD) were -1.04 and 1.70 l min^{-1} m^{-2}, since precision (SD) was 0.70 l min^{-1} m^{-2}. Hence, there was greater between-patient than within-patient variability.

Table 1 Patient characteristics

Patient	Age (years)	Sex	BMI (kg m^{-2})	CPB (min)	Surgery	Vasoactive drugs (μg kg^{-1} min^{-1})	EuroSCORE	R by CItp/CCIp
1	77	Male	28.0	99	CABG (x2)	Dopa 2	5	2/3
2	69	Male	29.6	59	CABG (x5)	–	2	1/2
3	63	Male	25.4	159	CABG (x4)	–	1	1/1
4	60	Male	25.7	91	CABG (x4)	Dobu 4	3	3/2
5	77	Male	33.2	75	CABG (x2)	Dopa 2	1	1/1
6	65	Female	30.1	113	CABG (x3)	Dopa 10	4	4/2
7	60	Male	23.9	52	CABG (x5)	Dopa 5	2	3/2
8	64	Male	31.3	168	CABG (x4)	Dobu 4 + Enox 2	2	3/4
9	84	Female	24.8	132	CABG (x3)	–	5	3/3
10	61	Male	30.8	85	CABG (x4)	Dobu 2	7	3/1
11	62	Male	28.7	149	CABG (x4)	Dopa 4	1	1/1

BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; Dobu, dobutamine; Dopa, dopamine; Enox, enoximone; R, number of rises (>5%) by CCIp, continuous pulmonary thermodilution cardiac index and CItp, transpulmonary thermodilution cardiac index, respectively.

Table 2 Haemodynamics prior to and after fluid loading steps

	$T=0$ ($n=11$)	$T=1$ ($n=11$)	$T=2$ ($n=10$)	$T=3$ ($n=10$)	$T=4$ ($n=9$)	$T=5$ ($n=8$)	P
HR (beats min^{-1})	80 ± 18	79 ± 18	80 ± 22	78 ± 17	79 ± 15	83 ± 17	0.017
MAP (mmHg)	76 ± 9	76 ± 9	77 ± 9	77 ± 9	73 ± 6	77 ± 9	0.001
PAOP (mmHg)	9 ± 3	10 ± 2	10 ± 3	9 ± 1	9 ± 1	10 ± 2	<0.001
CVP (mmHg)	9 ± 3	9 ± 3	10 ± 4	9 ± 2	9 ± 3	10 ± 3	<0.001
GEDVI (ml m^{-2})	875 ± 268	885 ± 270	896 ± 280	885 ± 237	901 ± 323	908 ± 310	0.135
CItp (l min^{-1} m^{-2})	3.6 ± 0.5	3.7 ± 0.7	3.8 ± 0.7	3.7 ± 0.6	3.8 ± 0.7	3.8 ± 0.5	<0.001
CCIp (l min^{-1} m^{-2})	3.2 ± 0.7	3.2 ± 0.6	3.2 ± 0.6	3.6 ± 1.0	3.5 ± 0.8	3.2 ± 0.5	0.043
Temperature (°C)	36.2 ± 0.5	36.1 ± 0.6	36.4 ± 0.6	36.5 ± 0.7	36.7 ± 0.8	36.8 ± 0.9	0.058

CCIp, continuous pulmonary thermodilution cardiac index; CItp, transpulmonary thermodilution cardiac index; CVP, central venous pressure; GEDVI, global end-diastolic volume index; HR, heart rate; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; $T=0$, before fluid loading; $T=1-5$, after each fluid-loading step. Mean ± SD and exact P, if greater than 0.001, for changes in time.

After excluding two patients with greatest within-patient variability between techniques (Fig. 1), CItp and CCIp correlated at $r=0.74$ ($P<0.001$; $n=49$) and changes in time at $r=0.63$ ($P<0.001$; $n=40$). Then, the bias was 0.38 l min^{-1} m^{-2} and limits of agreement (bias ± 2SD) were −0.55 and 1.29 l min^{-1} m^{-2}, since precision (SD) was 0.46 l min^{-1} m^{-2}. After correction for repeated measurements, bias was 0.21 l min^{-1} m^{-2} and limits of agreement (bias ± 2SD) were −1.14 and 1.56 l min^{-1} m^{-2}, since precision (SD) was 0.69 l min^{-1} m^{-2}, indicating almost unaltered between-patient variability.

For pooled data ($n=59$), CVP and GEDVI similarly correlated to CItp ($r=0.33$, $P=0.012$; $r=0.52$, $P<0.001$, respectively), whereas only CVP correlated to CCIp ($r=0.32$, $P=0.013$) and GEDVI did not ($r=0.24$, $P=0.064$). After excluding two patients with outliers of CItp versus CCIp (Fig. 1), the GEDVI still did not relate to CCIp ($r=0.18$, $P=0.231$; $n=49$), whereas the CVP did ($r=0.32$, $P=0.028$), and CVP and GEDVI both related to CItp ($r=0.37$ or higher, $P=0.010$ or lower). The PAOP did not relate to any of the variables except for CVP ($r=0.38$, $P=0.004$). Also, changes in GEDVI correlated to changes in CItp ($r=0.66$, $P<0.001$; $n=48$) but not to changes in CCIp ($r=0.12$, $P=0.435$; $P=0.002$ versus r for CItp) (Fig. 2), whereas changes in CVP did not relate to changes in either CCIp or CItp. In contrast, changes in CVP and GEDVI similarly related to those of CItp ($r=0.38$ or higher, $P=0.019$ or lower; $n=40$), after excluding two patients with CItp outliers (Fig. 1) and the rs did not differ from each other. Changes in PAOP only related to those in CVP ($r=0.51$, $P<0.001$). Table 4 shows that, for individual of triplicate measurements, changes in GEDVI best related to those in CItp (and not in CCIp) when derived from the same thermodilution curve.

Discussion

We compared the intermittent transpulmonary and the continuous pulmonary thermodilution techniques and associated measurements in predicting and monitoring fluid responses after coronary artery surgery. This allowed us to assess the dependency of the alleged superiority of filling volumes over pressures on cardiac output measurement techniques and their suitability to monitor fluid responses. We found fair overlap of cardiac output responses and relatively poor predictive and monitoring values of filling pressures. Mathematical coupling nevertheless overestimated the value, that is correlation with cardiac output (changes) of volumes over pressures, when derived from the same transpulmonary thermodilution curve as cardiac output.

The two cardiac output measurement techniques are supposedly less dependent on modulations of cardiac output by the mechanical respiratory cycle than bolus thermodilution measurements in the pulmonary artery. We found a fair correlation between CItp and CCIp and changes therein, in the absence of overt tricuspid regurgitation and rapid rewarming that may confound measurements. The limits of agreement were around or even above the 30% of the mean cardiac output, the criterion by Critchley and Critchley [29] for a clinically useful alternative to a standard technique, and lower after excluding two CItp outliers, with systematic overestimation (bias) by the transpulmonary technique as described before [4,19–23,25]. We cannot formally judge whether the relatively high limits of agreement, particularly after adjusting for within-patients variability, can be attributed to one technique or the other (or both), but our results suggest that the two patients with highest within-patient variability indeed had the greatest errors in CItp (versus CCIp), so that their exclusion hardly affected between-patients variability. Moreover, use of a Bland Altman analysis taking repeated measurements into account, thereby elevating limits of agreement in case of higher between-patient than within-patient variability, is not beyond criticism and the Critchley criterion may not apply [37]. Otherwise, the overestimation may partly relate to thermal loss [25], whereas the continuous thermodilution measurement does not carry such a problem. In spite of incomplete agreement of absolute values, the cardiac output response to fluid loading was similar among techniques, in accordance with the single prior

Table 3 Rises and no-rises among fluid-loading steps, by CItp and CCIp

	By CItp (>5% rises, $n=25$)		5% no-rises or less ($n=23$)		P	
	Before	After	Before	After	Baseline	Change
HR (beats min^{-1})	84 ± 19	83 ± 19	76 ± 17	75 ± 15	0.004	0.446
MAP (mmHg)	77 ± 10	76 ± 9	77 ± 10	75 ± 8	0.442	0.233
PAOP (mmHg)	9 ± 3	10 ± 3	9 ± 2	9 ± 2	0.559	0.785
CVP (mmHg)	9 ± 3	10 ± 3	8 ± 3	8 ± 3	0.096	0.319
GEDVI (ml m^{-2})	847 ± 246	914 ± 279	892 ± 294	854 ± 262	0.624	0.001
SVIcitp (ml m^{-2})	41 ± 10	48 ± 15	52 ± 13	49 ± 9	0.001	0.010
SVIccip (ml m^{-2})	36 ± 11	41 ± 16	46 ± 13	45 ± 11	0.001	0.046
CItp (l min^{-1} m^{-2})	3.3 ± 0.5	3.8 ± 0.7	3.8 ± 0.8	3.5 ± 0.6	0.006	n.a.
CCIp (l min^{-1} m^{-2})	2.9 ± 0.5	3.2 ± 0.8	3.4 ± 0.8	3.3 ± 0.7	0.005	<0.001
	By CCIp (>5% rises, $n=22$)		5% no-rises or less ($n=26$)			
	Before	After	Before	After		
HR (beats min^{-1})	82 ± 19	82 ± 20	79 ± 18	77 ± 15	0.622	0.158
MAP (mmHg)	77 ± 10	77 ± 10	74 ± 8	74 ± 7	0.297	0.329
PAOP (mmHg)	9 ± 3	10 ± 2	9 ± 2	9 ± 2	0.235	0.823
CVP (mmHg)	9 ± 3	9 ± 3	8 ± 3	9 ± 4	0.127	0.948
GEDVI (ml m^{-2})	938 ± 228	965 ± 249	810 ± 290	818 ± 273	0.070	0.939
SVIcitp (ml m^{-2})	45 ± 15	50 ± 16	47 ± 11	47 ± 9	0.729	0.021
SVIccip (ml m^{-2})	38 ± 13	46 ± 17	43 ± 13	41 ± 11	0.278	<0.001
CItp (l min^{-1} m^{-2})	3.5 ± 0.6	3.8 ± 0.7	3.6 ± 0.8	3.5 ± 0.6	0.467	0.001
CCIp (l min^{-1} m^{-2})	2.9 ± 0.5	3.5 ± 0.7	3.3 ± 0.8	3.0 ± 0.7	0.038	n.a.
	By CItp (≥10% rises, $n=14$)		Less than 10% no-rises ($n=34$)			
	Before	After	Before	After		
HR (beats min^{-1})	86 ± 16	85 ± 20	78 ± 18	77 ± 17	0.015	0.629
MAP (mmHg)	74 ± 8	75 ± 10	76 ± 9	76 ± 8	0.358	0.539
PAOP (mmHg)	10 ± 2	10 ± 2	8 ± 3	9 ± 2	0.180	0.961
CVP (mmHg)	9 ± 2	11 ± 22	8 ± 4	8 ± 3	0.368	0.165
GEDVI (ml m^{-2})	810 ± 255	916 ± 320	893 ± 274	872 ± 251	0.320	0.003
SVIcitp (ml m^{-2})	40 ± 9	50 ± 17	49 ± 13	47 ± 10	0.009	0.026
SVIccip (ml m^{-2})	35 ± 11	43 ± 19	43 ± 14	43 ± 12	0.066	0.063
CItp (l min^{-1} m^{-2})	3.3 ± 0.5	4.0 ± 0.7	3.6 ± 0.7	3.5 ± 0.6	0.116	n.a.
CCIp (l min^{-1} m^{-2})	2.9 ± 0.5	3.4 ± 0.9	3.2 ± 0.8	3.2 ± 0.7	0.308	0.010
	By CCIp (≥10% rises, $n=15$)		Less than 10% no-rises ($n=33$)			
	Before	After	Before	After		
HR (beats min^{-1})	76 ± 15	77 ± 21	82 ± 19	80 ± 17	0.180	0.595
MAP (mmHg)	75 ± 7	76 ± 8	76 ± 10	75 ± 9	0.600	0.725
PAOP (mmHg)	9 ± 3	10 ± 3	9 ± 2	9 ± 2	0.286	0.494
CVP (mmHg)	10 ± 4	10 ± 3	8 ± 3	9 ± 3	0.036	0.718
GEDVI (ml m^{-2})	901 ± 237	939 ± 240	854 ± 284	861 ± 283	0.578	0.509
SVIcitp (ml m^{-2})	46 ± 9	53 ± 16	46 ± 14	46 ± 10	0.892	0.086
SVIccip (ml m^{-2})	39 ± 11	50 ± 18	42 ± 14	40 ± 11	0.337	<0.001
CItp (l min^{-1} m^{-2})	3.4 ± 0.4	3.8 ± 0.5	3.6 ± 0.8	3.6 ± 0.7	0.114	0.002
CCIp (l min^{-1} m^{-2})	2.9 ± 0.5	3.6 ± 0.8	3.2 ± 0.7	3.1 ± 0.7	0.028	n.a.

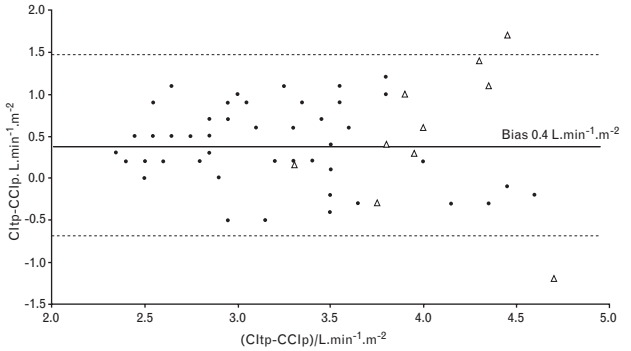
CCIp, continuous pulmonary thermodilution cardiac index; CItp, transpulmonary thermodilution cardiac index; CVP, central venous pressure; GEDVI, global end-diastolic volume index; HR, heart rate; MAP, mean arterial pressure; n.a., not applicable; PAOP, pulmonary artery occlusion pressure; SVIccip, stroke volume index from CCIp; SVIcitp, stroke volume index from CItp; mean ± SD and exact P, if greater than 0.001, for differences between rises and no-rises in baseline values and changes in fluid loading steps.

study on this issue [10], and, together with the high reproducibility of CCIp, this suggests that CCIp had reached a steady state after fluid-loading steps. Apparently, the 15 min observation period after each fluid loading step was sufficient to reach a steady state CCIp response, as noted before [26–28].

Fluid responses were not predicted or monitored well by filling pressures, in accordance with the literature [1,2,4–10,12,13], in spite of the low PEEP used in this study. Apparent superiority of CVP over PAOP can be explained if left ventricular function was well maintained after surgery. The poor value was independent of the manner to obtain and define fluid responses. In contrast, transpulmonary volumes have been claimed to better predict and monitor fluid responses than filling pressures, since, among others, fluid-induced changes better correlated with changes in transpulmonary stroke volume and cardiac output than pressures after cardiac surgery [1,2,4–10,12]. However, this has rarely been compared with an independent cardiac output measurement technique [10].

Our study suggests that the correlation between volumes and CItp changes which is greater than that between volumes and CCIp changes can be accounted for, at least

Fig. 1



Bland Altman plot for cardiac index measurements with help of the intermittent transpulmonary (CItp) and continuous pulmonary (CCIp) thermodilution techniques. Indicated are bias and upper and lower limits of agreement (bias ± 2SD). The two patients with greatest differences among techniques are indicated by triangles.

Table 4 Matrix of partial correlation coefficients of 36 fluid-induced changes (Δ) in individual (1–3) and mean of triplicate measurements of CItp and GEDVI, and CCIp

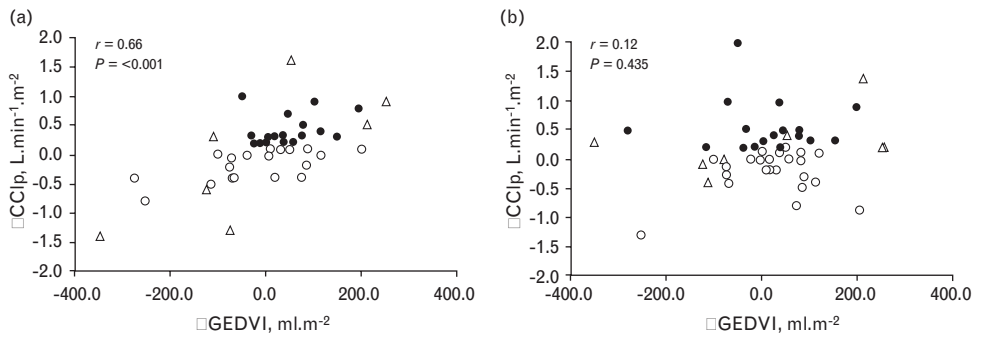
	ΔCItp1	ΔCItp2	ΔCItp3	$\Delta CItp_{mean}$	ΔCCIp
ΔGEDVI1	0.752*	0.526*	0.098	0.571*	0.089
ΔGEDVI2	0.421*	0.742*	0.046	0.515*	0.036
ΔGEDVI3	0.053	−0.127	0.602*	0.170	−0.087
$\Delta GEDVI_{mean}$	0.614*	0.628*	0.305	0.630*	0.231

The asterisks denote statistically significant relations ($P < 0.05$ or lower). Correlation coefficients at or below 0.421 are statistically significantly different ($P < 0.05$) from 0.752. CCIp, continuous pulmonary thermodilution cardiac index; CItp, transpulmonary thermodilution cardiac index; GEDVI, global end-diastolic volume index.

in part, by mathematical coupling of shared measurement error between CItp and volumes, when derived from the same thermodilution curve. The greater value of transpulmonary volumes than of filling pressures in monitoring (transpulmonary) cardiac output (changes) was abolished after excluding two patients with CItp outliers as compared to CCIp. Hence, the correlation between volumes and CItp was overestimated and spuriously increased over that with pressures. Indeed, a shared measurement error may spuriously increase a correlation coefficient when the range of observations is relatively small and/or the measurement error is relatively large [3,16–18]. However, animal and clinical studies [14,15], using the transpulmonary dilution technique, showed that cardiac output may change independently from volumes following infusion of inotropes or ß-blockers, but this does not exclude spurious covariance by mathematical coupling during fluid loading, when volumes and cardiac output change in the same direction. In comparing transpulmonary with continuous pulmonary thermodilution cardiac output measurements after coronary artery surgery, Hofer *et al.* [10] did not find overestimation of transpulmonary volumes over pressures as monitors of fluid responses based on mathematical coupling, in the absence of numerical data, perhaps because their fluid-induced increases in cardiac output were greater than in our study and the range of observations relative to measurement error was larger.

We did not include dynamic indicators to predict fluid responses in this study, because the goal was to compare static ones, and because dynamic indicators like stroke volume variations may also depend on ventilatory conditions [7,9,12,21,22,24,31]. The number of patients studied was relatively small, even after presuming fluid responses in 50% of steps, but apparently sufficient to demonstrate the effect of mathematical coupling. A formal power analysis was not considered feasible for

Fig. 2



Scatterplots showing the relationship between the fluid-induced changes of global end-diastolic volume index (GEDVI) and of transpulmonary (CItp, panel a) or continuous pulmonary (CCIp, panel b) thermodilution techniques: for CItp $r = 0.66$ ($P < 0.001$) and for CCIp $r = 0.12$ ($P = 0.435$; $P = 0.002$ for different r). The data of two patients with greatest difference between CItp and CCIp are indicated by triangles. Rises and no-rises among steps (≤5%, >5% CI increase) are indicated by closed and open symbols, respectively.

comparison of techniques to evaluate the role of mathematical coupling.

In conclusion, our data suggest that, in mechanically ventilated patients after coronary artery surgery, fluid responses can be assessed by either intermittent transpulmonary or continuous pulmonary thermodilution measurements of cardiac output. Whereas filling pressures are poor predictors and monitors of fluid responses, the superiority of transpulmonary volumes over filling pressures can be overestimated by mathematical coupling of a shared measurement error when derived from the same transpulmonary thermodilution curve as cardiac output.

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